FLUORINATED ANALOGUES OF TRICYCLIC NEUROLEPTICS: 6,9-DIFLUORO DERIVATIVE OF 10-(4-METHYLPIPERAZINO)--10,11-DIHYDRODIBENZO[*b,f*]THIEPIN*

Irena ČERVENÁ, Marta HRUBANTOVÁ, Emil SVÁTEK, Jiří HOLUBEK, Miroslav RYSKA, Jiřina METYŠOVÁ and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

Received February 11th, 1980

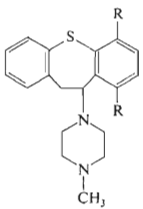
The acid *VI*, obtained from 2,5-difluorothiophenol (*IV*) and (2-iodophenyl)acetic acid, afforded by cyclization with polyphosphoric acid 6,9-difluorodibenzo[*b,f*]thiepin-10(11*H*)-one (*VII*) in a satisfactory yield. Two further steps led to the chloro derivative *X* giving by a substitution reaction with 1-methylpiperazine the title compound *III*. This substance exhibits some 10% incoordinating activity of the unsubstituted compound *I* and an indication of cataleptic activity, in contrast to the inactive analogous dichloro compound *II*. The bulky atom of chlorine in the vicinity of the methylpiperazine residue interferes evidently with the CNS activity; the influence of the atom of fluorine is much less pronounced in this line.

In the course of investigations of the influence of fluorination in aromatic positions in molecules of the 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins on the neuroleptic activity (for preliminary discussion of this problem[1-3]), one important direction was represented by the synthesis of fluorinated derivatives of the otherwise unsubstituted 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*I*), perathiepin[4-6]. Out of the fluoro derivatives of this compound, the following were described in the meantime: 2-fluoro[7], 3-fluoro[8], 6-fluoro[9], 7-fluoro[10], 8-fluoro[11] and 7,8-difluoro compound[12]. The information on the influence of fluorination in position 9 has thus been lacking until now. In analogy with the corresponding 9-chloro derivative[13] it was necessary to expect difficulties also for the synthesis of the 9-fluoro compound. It has been found that [2-(3-fluorophenylthio)phenyl]acetic acid cyclizes exclusively to 7-fluorodibenzo[*b,f*]thiepin-10(11*H*)-one. Therefore, the usual synthetic approach could not be applied for the synthesis of the 9-fluoro derivative of compound *I*. Because of the fact that the influence of fluorination in position 6 on the activity has been determined[9] (it maintains the central depressant activity, lowers the cataleptic one), we selected, for obtaining the first information about the influence of fluorination in position 9, a compound containing fluorine atoms in posi-

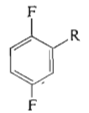
* Part CXLII in the series Neurotropic and Psychotropic Agents; Part CXLI: This Journal *45*, 1086 (1980).

tions 6 and 9, *i.e.* the title compound *III* for which the synthetic accessibility on the usual preparative route could be expected. We thus entered a similar way like in the case of the 9-chloro compound when the corresponding 6,9-dichloro derivative[14] has been synthesized in the first line.

Similar methods like in the preparation of the other perathiepin derivatives fluorinated in the ring C (ref.[9-12]) were used in the synthesis of compound *III*. The starting compound was 2,5-difluorothiophenol (*IV*) which was prepared in a low yield from 2,5-difluoroaniline[15] by the xanthate method (analogy[16]). The main product was a sulfur-free compound, insoluble in aqueous potassium hydroxide, for which the mass spectrum indicated the composition of $C_{12}H_7F_4N_3$. The product was identified as the triazene derivative *V*. The formation of triazenes as by-products of diazotization of aromatic amines is a common phenomenon[17] and it was mentioned also by our group earlier[18,19]. The reaction of the thiophenol *IV* with (2-iodophenyl)-acetic acid[20] in a boiling solution of potassium hydroxide in the presence of copper afforded the acid *VI*.

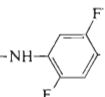


I, R = H
II, R = Cl
III, R = F

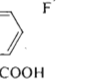


IV, R = SH

V, R = N=N–NH–



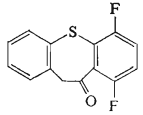
VI, R = S–



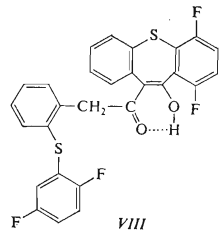
The acid *VI* was cyclized with polyphosphoric acid at 125°C (mentioned in a preliminary way in[21]; for the cyclization of the analogous dichloro acid much higher temperature was necessary[14]). The desired 6,9-difluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VII*) was obtained in a satisfacactory yield. Due to steric reasons, the cyclization proceeds in this case much easier than in the case of the analogous dichloro acid[14]. Chromatography of the mother liquor gave a small amount of a single by-product $C_{28}H_{16}F_4O_2S_2$. This composition indicates that we are dealing here with a product of acylation of the ketone *VII* with one further molecule of the acid *VI*. With a product of a similar type we met already in the cyclization of [2-(4-chlorophenylthio)-4,5-dimethoxyphenyl]acetic acid[22] and on the basis of a band at 1754 cm^{-1} in its IR spectrum we assigned to it the structure of the O-acylated product, *i.e.* of the enol ester. The IR spectrum of the product presently obtained does not show the mentioned band; on the other hand it shows a typical band at 1610 cm^{-1}

corresponding to a conjugated keto group hydrogen-bonded to the enol. The product is therefore formulated as the C-acylated compound *VIII*. This formula is supportedl by the ^{1}H-NMR spectrum. Similar structures were assigned to products of reactions of 4,4'-dichlorodiphenyl sulfide and similar diaryl sulfides with chloroacetyl chloride and aluminium chloride[21,23].

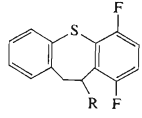
Reduction of the ketone *VII* with sodium borohydride in aqueous ethanol gave the alcohol *IX* which was transformed by treatment with hydrogen chloride in benzene at room temperature to the chloro derivative *X*. Its substitution reaction with 1-methylpiperazine in boiling chloroform resulted in the base *III* in a high yield. The neutral by-product, isolated in a small amount, was identified as 1,4-difluorodibenzo[*b*,*f*]thiepin (*XI*), *i.e.* product of the elimination reaction.



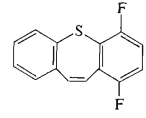
VII



VIII



IX, R = OH
X, R = Cl



XI

Compound *III* was pharmacologically tested in the form of the soluble methanesulfonate on parenteral administration. In the rotarod test in mice on intravenous administration, the incoordinating activity corresponding to the central depressant effect was followed. The medium effective dose (ED_{50}) brings about ataxia in 50% mice in the time of maximum activity. The cataleptic activity was evaluated in the test in rats on intraperitoneal administration; the medium effective dose (ED_{50}) brings about catalepsy in 50% animals in the group. The results are given in Table I including for comparison perathiepin (*I*) and its 6,9-dichloro derivative *II*; the doses were calculated for the bases. The comparison shows that the 6,9-difluoro derivative is less active in both of the tests than perathiepin: in the rotarod test it has only

some 10% perathiepin activity and in the test of catalepsy, a dose corresponding to 200% of the perathiepin ED_{50}, brings about catalepsy in 30% animals only. On the other hand, the analogous 6,9-dichloro compound *II* was inactive in both of the tests in the dose given. We have to conclude that the bulky substituent on the aromatic ring in the close vicinity of the methylpiperazine residue influences very unfavourably the central activity. The atom of fluorine, being substantially smaller than the chlorine atom, has a lower unfavourable effect.

EXPERIMENTAL

The melting points of analytical preparations were determined in an automatic Mettler FP-5 melting point recorder. The samples were dried at about 50 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (mostly in $CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer, ^{19}F-NMR spectra (in $CHCl_3$, $\delta CFCl_3 = 0$) with the same instrument, and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel (Silufol).

2,5-Difluorothiophenol (*IV*)

2,5-Difluoroaniline[15] (39·4 g, b.p. 72°C/1·6 kPa) was added dropwise under stirring to 120 ml 1 : 1 dilute hydrochloric acid, the suspension of hydrochloride obtained was cooled to —3—0°C and diazotized with a solution of 21·4 g $NaNO_2$ in 50 ml water added dropwise. The mixture was stirred for 30 min with cooling and then dropped over 2 h into a stirred solution of 58 g potassium ethyl xanthate in 72 ml water kept at 40—45°C. After 2 h stirring at room temperature, the mixture was allowed to stand overnight and extracted with ether. The organic layer was washed with water, ether was distilled off, the residue was dissolved in 200 ml boiling ethanol and the solution was treated over 1 h with 75 g KOH. The mixture was refluxed for 12 h, ethanol was evaporated *in vacuo*, the residue was mixed with 200 ml water and the insoluble product extracted with ether. The aqueous layer was treated with 5 g Zn and acidified with hydrochloric acid. The product was extracted with ether, the extract dried with Na_2SO_4, evaporated and the

TABLE I
Pharmacological Comparison of Compounds *I*—*III*

Compound	Name or code number	Ref.	Rotarod ED_{50} *i.v.* mg/kg	Catalepsy ED_{50} *i.p.* mg/kg
I	Perathiepin	24	0·19	10
II	VÚFB-9464	14	>10	>10
III	VÚFB-13716	—	1·6	>20 (30%)

residue distilled; 11·1 g (25%), b.p. 60—62°C/2 kPa. For $C_6H_4F_2S$ (146·2) calculated: 49·30% C, 2·76% H, 26·00% F, 21·94% S; found: 49·78% C, 2·92% H, 26·68% F, 22·39% S.

1,3-Bis(2,5-difluorophenyl)triazene (*V*)

The ethereal solution, obtained in the preceding experiment by extraction of the alkaline mixture, was evaporated and gave 17·5 g (43%) product, m.p. 153—157°C. Analytical sample, m.p. 156—157°C (ethanol–ether). UV spectrum: λ_{max} 282 nm (log ε 3·72), 356 nm (4·34). IR spectrum: 810, 863, 878 (2 adjacent and solitary Ar—H), 1 502, 1 531 (Ar), 1 634 (N=N), 3 085 (Ar), 3 318 cm^{-1} (NH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 13·08 (s, 1 H, NH), 6·80—7·80 (m, 6 H, Ar—H). Mass spectrum, *m/e* (%): 269·0588 (M^+, corresponds to $C_{12}H_7F_4N_3$), 241 (15), 141 (100), 128 (40), 113 (100), 101 (60), 63 (100). For $C_{12}H_7F_4N_3$ (269·4) calculated: 53·49% C, 2·62% H, 28·21% F, 15·68% N; found: 53·52% C, 2·80% H, 28·62% F, 15·85% N.

[2-(2,5-Difluorophenylthio)phenyl]acetic Acid (*VI*)

IV (10·8 g) was stirred for 10 min with a solution of 15 g KOH in 150 ml water, the mixture was treated with 19·3 g (2-iodophenyl)acetic acid[20] and 0·7 g copper, and refluxed under stirring for 16 h. It was filtered while hot and the filtrate was acidified with hydrochloric acid. The precipitated product was filtered after standing for 24 h; 13·3 g (64%), m.p. 66—80°C. Analytical sample, m.p. 84—85°C (aqueous ethanol). IR spectrum: 762, 771, 810, 825, 866 (4 and 2 adjacent and solitary Ar—H), 930, 1 189, 1 241, 1 704, 2 560, 2 740 (COOH), 1 481, 1 588, 1 613, 3 020, 3 068, 3 085 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 11·30 (bs, 1 H, COOH), 7·20—7·60 (m, 4 H, Ar—H in the phenylacetic acid residue), 6·30—7·10 (m, 3 H, remaining Ar—H), 3·82 (s, 2 H, $ArCH_2$). ^{19}F-NMR spectrum: δ —117·9 and —118·4 (2 m, 2 F). For $C_{14}H_{10}F_2O_2S$ (280·3) calculated: 59·99% C, 3·59% H, 13·56% F, 11·42% S; found: 60·00% C, 3·77% H, 13·77% F, 11·70% S.

6,9-Difluorodibenzo[*b,f*]thiepin-10(11*H*)-one (*VII*)

A mixture of 7·6 g *VI* and 75 g polyphosphoric acid was stirred for 2·5 h at 120—125°C. After cooling it was decomposed with water and extracted with benzene. The extract was washed with 5% NaOH and water. Acidification of the alkaline solution recovered 1·5 g starting *VI*, m.p. 76—82°C. The washed extract was dried with $CaCl_2$ and evaporated; 5·5 g (96% per conversion), m.p. 125—138°C. The crude product was crystallized from a mixture of benzene and light petroleum, 3·60 g, m.p. 137—140°C. Analytical sample, m.p. 138—139°C. UV spectrum: λ_{max} 330 nm (log ε 3·71), infl. 245 nm (4·41). IR spectrum (KBr): 753, 821 (4 and 2 adjacent Ar—H), 1 448 (C—H in CH_2CO), 1 568, 1 607, 3 070 (Ar), 1 693 cm^{-1} (CO—Ar). For $C_{14}H_8F_2OS$ (262·3) calculated: 64·11% C, 3·07% H, 14·49% F, 12·22% S; found: 64·16% C, 3·26% H, 14·55% F, 12·41% S.

Chromatography of the mother liquors on a column of 60 g neutral Al_2O_3 (activity II) under elution with benzene gave 0·7 g ketone *VII*, m.p. 134—137°C. Elution with benzene containing 5% ethanol gave 0·25 g 6,9-difluoro-11-[2-(2,5-difluorophenylthio)phenyl]acetyldibenzo[*b,f*]thiepin-10-ol (*VIII*), m.p. 146—148°C (benzene–light petroleum). Mass spectrum, *m/e* (%): 524·0599 (20, M^+, corresponds to $C_{28}H_{16}F_4O_2S_2$), 289 (100), 261 (20), 235 (10), 232 (40). UV spectrum: λ_{max} 243 nm (log ε 4·40), 282 nm (4·06), 325 nm (4·10). IR spectrum (KBr): 763, 820, 869 (4 and 2 adjacent and solitary Ar—H), 1 250 (Ar—F), 1 483, 1 560, 1 590, 3 065, 3 085 (Ar), 1 610 cm^{-1} (CO—C=C—OH). ^{1}H-NMR spectrum: δ 16·51 (s, 1 H, C=C—OH), 6·10—7·60 (m, 13 H, Ar—H), 4·12 and 3·82 (ABq, J = 17·0 Hz, 2 H, $ArCH_2$). For $C_{28}H_{16}F_4O_2S_2$ (524·6) calculated: 64·11% C, 3·07% H, 14·49% F, 12·22% S; found: 65·00% C, 3·31% H, 14·55% F, 12·46% S.

6,9-Difluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IX*)

A solution of 5·2 g *VII* in 95 ml ethanol and 20 ml benzene was stirred and treated dropwise with a solution of 0·26 g $NaBH_4$ in 2·3 ml water containing 0·5 ml 1% NaOH. The mixture was stirred and refluxed for 4 h, the solvents were evaporated *in vacuo*, the residue diluted with water and extracted with benzene. The extract was washed with 3% NaOH and water, dried (Na_2SO_4), evaporated *in vacuo* and the residue crystallized from a mixture of benzene and light petroleum; 4·9 g (94%), m.p. 122-124°C. Analytical sample, m.p. 123—124°C. IR spectrum: 761, 822 (4 and 2 adjacent Ar—H), 1 042, 1 056, 1 070 (CHOH in the cycle), 1 609 (Ar), 3 420 cm^{-1} OH). ^{1}H-NMR spectrum: δ 6·60—7·70 (m, 6 H, Ar—H), 5·30 (bm, J(H—OH) = 6·0 Hz, 1 H, Ar—CH—O), 3·70 and 3·50 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·30 (dd, disappears after D_2O, J(OH—F) = 3·0 Hz, 1 H, OH). ^{19}F-NMR spectrum: δ —112·5 (m, 1 F, 6-F), —118·8 (m, 1 F, 9-F). For $C_{14}H_{10}F_2OS$ (264·3) calculated: 63·62% C, 3·81% H, 14·38% F, 12·13% S; found: 64·02% C, 3·98% H, 14·47% F, 12·29% S.

11-Chloro-1,4-difluoro-10,11-dihydrodibenzo[*b,f*]thiepin (*X*)

A solution of 4·9 g *IX* in 50 ml benzene was saturated for 5 h with anhydrous HCl in the presence of 5 g $CaCl_2$ at room temperature. After standing overnight the mixture was filtered and the filtrate evaporated; 5·1 g (97%), m.p. 109—110°C. Analytical sample, m.p. 110·3—110·7°C (benzene–light petroleum). ^{1}H-NMR spectrum: δ 7·55 (mcd, 1 H, 6-H), c 7·25 (m, 3 H, 7,8,9-H_3), c. 6·90 (m, 2 H, 2,3-H_2), 5·68 (dd, 1 H, Ar—CH—Cl), 3·82 (m, 2 H, $ArCH_2$). For $C_{14}H_9ClF_2S$ (282·7) calculated: 59·47% C, 3·21% H, 12·54% Cl, 13·44% F, 11·34% S; found: 59·44% C, 3·21% H, 12·57% Cl, 13·71% F, 11·10% S.

1,4-Difluoro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*III*)

A mixture of 4·7 g *X*, 6·7 ml 1-methylpiperazine and 10 ml chloroform was refluxed for 8 h. The solvent was evaporated, the residue diluted with water and extracted with benzene. The extract was washed with water and then shaken with 100 ml 3M-HCl. The precipitated hydrochloride was filtered, suspended in the aqueous layer of the filtrate, the suspension made alkaline with NH_4OH and the base extracted with benzene. The extract was dried with K_2CO_3 and evaporated; 3·86 g (67%) base, m.p. 136—140°C. Analytical sample, m.p. 140—141°C (benzene–light petroleum). UV spectrum: λ_{max} 222 nm (log ε 3·98), 259 nm (3·75), 291 nm (3·72). IR spectrum (KBr): 765, 810, 820 (4 and 2 adjacent Ar—H), 1 230 (Ar—F), 1 450 (CH_2), 1 572, 1 609, 3 060, 3 088 (Ar), 2 740, 2 772, 2 798 cm^{-1} (N—CH_3). ^{1}H-NMR spectrum: δ 6·60—7·70 (m, 6 H, Ar—H), 3·00—4·50 (m, 3 H, $ArCH_2CHAr$), 2·62 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·30 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·18 (s, 3 H, N—CH_3). ^{19}F-NMR spectrum: δ —107·5 (m, 1 F, 4-F), —108·3 (m, 1 F, 1-F). For $C_{19}H_{20}F_2N_2S$ (346·4) calculated: 65·87% C, 5·82% H, 10·97% F, 8·09% N, 9·25% S; found: 66·41% C, 5·94% H, 10·70% F, 7·94% N, 9·26% S.

Methanesulfonate, m.p. 239—241°C (ethanol–ether). For $C_{20}H_{24}N_2O_3S_2$ (442·5) calculated, 54·28% C, 5·47% H, 8·59% F, 6·33% N, 14·49% S; found: 54·45% C, 5·68% H, 8·76% F, 6·27% N: 14·65% S.

The benzene layer of the filtrate after the hydrochloride was washed with dilute hydrochloric acid and water, dried and evaporated. The residue was crystallized from ethanol; 0·85 g (21%) 1,4-difluorodibenzo[*b,f*]thiepin (*XI*), m.p. 107—111°C. Analytical sample, m.p. 110—112°C. UV spectrum: λ_{max} 256·8 nm (log ε 4·26), 305 nm (3·94). IR spectrum: 729, 749, 800, 820 (4 and 2 adjacent Ar—H), 774 (*cis*-CH=CH), 1 234 cm^{-1} (Ar—F). ^{1}H-NMR spectrum: δ 6·70—7·80 (m, Ar—H and CH=CH). ^{19}F-NMR spectrum: δ —115·2 and —119·5 (2 m, 2 F). For $C_{14}H_8F_2S$

(246·3) calculated: 68·28% C, 3·27% H, 15·43% F, 13·02% S; found: 68·06% C, 3·62% H, 15·30% F, 13·20% S.

The authors are indebted to Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs J. Kropáčová (analytical department of this institute) for carrying out the analyses.

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Translated by the author (M. P.).